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Identification of Early Cellular Immune Factors Regulating Growth of Malaria Parasites in Humans

In many host-parasite systems, regulatory T cells ($CD4^+$, $CD25^+$, $FOXP3^+$) have been shown to modulate cellular immunity and pathology. In this issue of *Immunity*, Walther et al. have now shown that following experimental malaria infection of human volunteers, enhanced TGF-β and T reg responses are associated with a faster parasite growth rate. The study demonstrates that regulation of cellular immunity must be addressed if we are to develop successful interventions.

The ability of cellular immune responses to control the growth of the blood stages of malaria parasites is thought to be critical to disease outcome (Grun and Weidanz, 1983; Good et al., 2005). Although red blood cells express few if any MHC antigens and cannot be directly recognized by T cells, it is thought that parasites are destroyed by small inflammatory molecules downstream of T cells activated by presented antigen, predominantly in the spleen. Since parasite density is a key index of disease outcome, it is reasonable to expect that those factors that regulate the cellular immune responses to malaria will have a major bearing on morbidity and mortality.

However, disease outcome involves more than parasite killing per se, because inflammatory parasiticidal molecules may also contribute to disease. Inflammatory cytokines are involved in the pathogenesis of cerebral malaria, anemia, and other organ pathologies. In a rodent model, antibodies to IFN-γ can prevent cerebral malaria (Grau et al., 1989), and it has been shown that while $CD4^+$ Th1 cells could transfer resistance to parasite growth, those mice that received the most T cells died earliest with weight loss and anemia (Hirunpetcharat et al., 1999).

It seems that if inflammatory processes could be judiciously boosted to control parasite growth, disease might be prevented; alternatively, inhibition of inflammatory responses might lessen disease irrespective of parasite load. In many systems, regulatory T cells have been shown to determine the balance between pathology and the microbial killing that follows activation of cellular immunity (Belkaid and Rouse, 2005). TGF-β, often produced during chronic infections, is thought to be important in T reg induction, function, and survival. However, its function in malaria immunity and immunopathology is not well understood.

For example, following infection with the rodent parasite, *Plasmodium berghei*, TGF-β levels are inversely related to parasite burden, whereas during *P. chabaudi* and *P. yoelii* infections, levels initially decrease with increasing parasitemia but then increase (Omer and Riley, 1998). Recombinant TGF-β therapy could significantly reduce parasite load; however, this effect was not dose dependent and was difficult to explain given its antiinflammatory properties. In a separate study of the correlation of TGF-β levels and parasitemia, Su et al. (2005) observed that mice coinfected with *P. chabaudi* and a nematode had higher TGF-β levels and a higher parasite burden than mice infected with *P. chabaudi* alone. In keeping with these data, Hisaeda et al. (2004), while not examining the TGF-β response, did observe that depleting T reg cells in vivo enabled mice to control an otherwise lethal infection with *P. yoelii.* These various studies, while somewhat conflicting, point to a role for TGF-β in regulating parasite burden.

The TGF-β response has also been shown to differ between mice infected with a virulent *Plasmodium* strain and those infected with a benign strain. Thus, Omer et al. (2003) demonstrated that following infection with the avirulent *P. yoelii 17X*, TGF-β levels peaked late and correlated with reduced parasite density, whereas infection with the virulent *P. yoelii 17XL* resulted in an early TGF-β response, a downregulated Th1 response, failure to clear parasites, and death. Furthermore, the TGF-β response per se may dictate whether a given infection follows a virulent course: blocking TGF-β in vivo can shorten survival time with only a modest increase in parasitemia (Omer and Riley, 1998). These data demonstrate a complex duality of immunoregulatory effects of TGF-β with respect to parasite burden and pathology. Defined clinical studies are needed to gauge the relevance of TGF-β in human malaria.

Walther et al. (2005) have now studied immunological correlates of parasitemia in 26 individuals (half of whom had received a candidate liver-stage vaccine) following experimental infection with genetically identical malaria sporozoites. While the vaccine did not protect, it provided the investigators with a relatively large group of malaria-naive individuals for whom parasite growth rates were available following infection and in whom immune responses could be determined. Following infection, half of the individuals demonstrated an early peak in plasma TGF-β levels, and those individuals had a significantly higher parasite growth rate. The response was unrelated to whether or not the individuals received the vaccine. The TGF-β response correlated with a boost in $CD25^+$ $FOXP3^+$ T reg cell numbers. In vitro depletion of $CD25^+$ cells resulted in an enhanced proliferative and IFN-γ T cell response to parasite antigens. The data are consistent with early control of parasite growth by a $CD4^+$ T cell-derived IFN-γ response that can be modulated by T reg cells downstream of TGF-β induction.

The study is looking only at the very early regulatory responses following infection. These may set the course of the unfolding immune response and ultimate outcome. However, the effect of the regulatory responses later in infection may be different but equally important. Chaiyaroj et al. (2004) observed that TGF-β levels were lower in individuals with uncomplicated malaria than in healthy controls and lower again in severe malaria. The infection had progressed much further in these patients than in the experimental subjects of Wal-

ther et al., but the low TGF-β response in cases of severe malaria (who also had the highest parasite burdens) are likely to represent a failure of the regulatory response to dampen host pathology late in infection. Understanding the nature of the TGF-β response throughout infection should yield important insights into immunity and pathogenesis.

The paper raises many questions relevant to pathogenesis. Foremost is why only some individuals generate a TGF-β response and whether such individuals would ultimately demonstrate a worse outcome (had the infection been allowed to proceed). The authors suggest a genetic basis for the variation in response, but their data do not exclude that the response is stochastic. This could be explored by reexposing the same individuals to another infection and observing whether the same TGF-β response followed. Identification of the parasite molecule(s) responsible for stimulating TGF-β production is an important challenge and could lead to novel therapies relevant not only to malaria but to many diseases. It is also important to identify the source of TGF-β. While their data point to monocytes as a likely source within peripheral blood, non-blood cells such as hepatocytes cannot be excluded, particularly since infection commenced with a sporozoite inoculation, which is immediately followed by a liver phase. It is also not clear whether TGF-β transformed conventional $CD4^+$ T cells to become T regs (Chen et al., 2003) or whether natural T reg cells are activated by *Plasmodium* to produce TGF-β.

The demonstration of a correlation between early parasite growth rates and parameters of immune regulation provides new insight into human immune surveillance of malaria that will be invaluable for vaccine and possibly drug development to combat malaria.

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